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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/CA94/00518 <b>(22) International Filing Date:</b> 21 September 1994 (21.09.94) <b>(30) Priority Data:</b> 125,372 21 September 1993 (21.09.93) US <b>(60) Parent Application or Grant</b> <b>(63) Related by Continuation</b> US 125,372 (CON) Filed on 21 September 1993 (21.09.93) <b>(71) Applicant (for all designated States except US):</b> MERCK FROSST CANADA INC. [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Quebec H9H 3L1 (CA). <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> BECHARD, Simon, R. [CA/CA]; 1755 Marchand Street, Laval, Quebec H7G 4V7 (CA). <b>(74) Agents:</b> MURPHY, Kevin, P. et al.; Swabey Ogilvy Renault, Suite 800, 1001 de Maisonneuve Boulevard West, Montreal, Quebec H3A 3C8 (CA).		<b>(81) Designated States:</b> AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> ENTERIC COATED ORAL COMPOSITIONS CONTAINING BISPSPHONIC ACID DERIVATIVES		
<b>(57) Abstract</b>  The present invention relates to a novel oral dosage form of a bisphosphonic active ingredient for use in treatment of diseases involving bone resorption and formulated in an enteric-coated form for administration to subjects exhibiting upper gastrointestinal tract sensitivity to bisphosphonic acid compounds.		

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TITLE OF THE INVENTION

ENTERIC COATED ORAL COMPOSITIONS CONTAINING  
BISPHOSPHONIC ACID DERIVATIVES

5 SUMMARY OF THE INVENTION

10 The present invention relates to a novel oral dosage form of a bisphosphonic active ingredient for use in treatment of diseases involving bone resorption and formulated in an enteric-coated form for administration to subjects exhibiting upper gastrointestinal tract sensitivity to bisphosphonic acid compounds. Said novel dosage form consists of a core tablet containing a therapeutically effective amount of a bisphosphonic acid active ingredient which is subcoated with a polymeric film having the effect of preventing migration of active ingredient from core tablet to the outer enteric coating. This subcoat improves product stability by minimizing drug interaction with the acidic enteric coating and also permits application of an enteric coating sufficiently thin to rapidly and completely dissolve upon entry into the proximal portion of the lower gastrointestinal tract.

20 BACKGROUND OF THE INVENTION

The bisphosphonates are a new class of drugs which have been developed during the past two decades for diagnostic and therapeutic use in various diseases of bone and calcium metabolism. Papapoulos describes therapeutic bisphosphonates as falling into three categories: first generation drugs typified by etidronate, which have significant activity but do not predictably suppress bone resorption; second generation agents such as pamidronate which cause predictable resorption suppression when given parenterally, but are hampered in oral formulations by low absorption and GI toxicity, and a third generation with both oral and parenteral efficacy. Fleisch indicates that bisphosphonate compounds are the drugs of choice in tumor induced bone disease and that the relatively few adverse events that have been associated with their use are specific for each compound.

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The three compounds commercially available for use in tumor induced bone disease are in order of increasing potency, 1-Hydroxyethylidene-bisphosphonic acid (etidronate), Dichloromethylene-bisphosphonic acid (clodronate), and 3-Amino-1-hydroxypropylidene-bisphosphonic acid (pamidronate). Other bisphosphonate compounds known in literature to have been administered to humans include 4-Amino-1-hydroxybutylidene-bisphosphonic acid (alendronate), 6-Amino-1-hydroxyhexylidene-bisphosphonic acid, Chloro-4-phenylthio-methylidene-bisphosphonic acid (tiludronate), 2-(3-pyridinyl)-1-hydroxyethylidene-bisphosphonic acid (risedronate), and 1-Hydroxy-3(methylpentylamino)-propylidene-bisphosphonic acid (BM 21.0955).

The individual bisphosphonates exhibit varying degrees of gastrointestinal toxicity. The pronounced GI toxicity of pamidronate is well documented and use of enteric coated tablets of pamidronate in clinical studies was disclosed by Reid *et al.* PCT Publication No. WO 93/09785 discloses enterically-coated dosage forms of the drug risedronate, one embodiment of which is a compressed tablet of active ingredient directly coated with a single layer of enteric polymer. The absence of prior art suggesting enteric coated dosage forms for bisphosphonates other than pamidronate and risedronate may reflect lower degrees of G.I. toxicity exhibited by some of these compounds or the fact that the low absorption of some of these compounds through the gastrointestinal tract has made IV infusion the favored mode of administration. The greater antihypercalcemic activity and GI absorption of newer compounds makes oral administration increasingly attractive. Although these other bisphosphonates may not exhibit the same degree of GI toxicity as pamidronate, they nonetheless may produce gastric irritation in particularly sensitive individuals. Enteric-coated dosage forms for these other bisphosphonate compounds may provide a solution to this problem. In order to maximize absorption of active, it is desirable that such a dosage form release the active in the proximal portion of the lower G.I. tract, preferably in the small intestine. This requires that the enteric film be soluble at pH 5.5 or greater as typically present in the small and large intestines. Enteric coated dosage forms can suffer from

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stability problems as a result of interactions between the active drug and the acidic enteric coating. In particular, bisphosphonate compounds which have a basic nitrogen containing moiety are susceptible to interaction with acidic carboxyl groups present in the enteric coating polymer. The present invention solves the above problems by providing a novel enteric-coated dosage form comprising a core tablet containing a therapeutically effective amount of bisphosphonate, a stability enhancing subcoat which minimizes migration of active from core tablet to the surface of the enteric coating, and an enteric film specifically formulated to rapidly and completely dissolve once the dosage form enters the proximal portion of the lower gastrointestinal tract.

#### DETAILED DESCRIPTION OF THE INVENTION

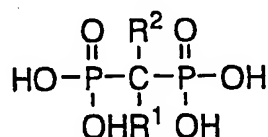
This invention relates to a novel enteric-coated dosage form of a bisphosphonic acid active ingredient adapted for oral administration to subjects suffering from metabolic bone diseases (e.g. osteoporosis) including those associated with abnormal calcium metabolism e.g. hypercalcemia and exhibiting upper gastrointestinal tract sensitivity to bisphosphonic acid. Said dosage forms comprise a pH dependent enteric film formulated to rapidly and completely dissolve upon exposure to intestinal fluids having a pH of 5.5 or greater, and a stability enhancing polymeric subcoat deposited on a core tablet containing the bisphosphonate active ingredient. Dosage forms of this invention prohibit the release of active ingredient in the mouth, esophagus, and stomach and thereby protect mucosal tissues thereof from irritation that may result from exposure to bisphosphonic acid compounds. Accordingly, the said dosage form effects the delivery to the proximal portion of lower intestinal tract of a safe and effective amount of bisphosphonic acid active ingredient while minimizing irritation of the mouth, esophagus, and stomach that may accompany the oral administration of bisphosphonic acid compounds.

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A. The Bisphosphonate Active Ingredient

The scope of this invention covers those bisphosphonic acid compounds corresponding to structural Formula (I)

5



(I)

10

or any pharmaceutically acceptable salt thereof, wherein:

R<sup>1</sup> is

- (a) C<sub>1-5</sub> alkyl, unsubstituted or substituted with:
- (1) NH<sub>2</sub>,
- (2) pyridyl,
- (3) pyrrolidyl,
- (4) NR<sup>3</sup>R<sup>4</sup>;
- (b) NR<sup>5</sup>,
- (c) SR<sup>6</sup>,
- (d) Cl;

20

R<sup>2</sup> is H, OH, Cl;R<sup>3</sup> is H, C<sub>1-4</sub> alkyl;R<sup>4</sup> is C<sub>1-4</sub> alkyl;R<sup>5</sup> is C<sub>1-10</sub> alkyl;

25

R<sup>6</sup> is aryl.

Methods for the preparation of various bisphosphonic acid compounds may be found in, e.g., U.S. Patent No. 3,962,432;

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U.S. Patent No. 4,054,598; U.S. Patent No. 4,327,039;U.S. Patent No. 4,621,077; U.S. Patent No. 4,746,654;U.S. Patent No. 4,267,108; U.S. Patent No. 4,407,761;U.S. Patent No. 4,624,947; U.S. Patent No. 4,922,077;and EPO Patent Pub. No. 0,252,504.

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A particular illustration of the present invention is the novel dosage form thereof in which the bisphosphonic acid active ingredient is 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid (alendronate).

Further exemplifying the present invention is the novel dosage form thereof containing the sodium salt of 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid, in particular 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate. Studies indicate that, when parenterally administered, this compound is about five times more effective in reducing hypercalcemia associated with tumor induced bone disease in humans than pamidronate, the most potent bisphosphonate commercially available for treatment of tumor induced bone disease. 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid and its homologs in which the R<sup>1</sup> side chain is a N-alkyl group varying in length from 1 to 5 carbon atoms and terminally substituted with an amino group may be readily synthesized according to methods disclosed in US Patents 4,407,761, and 4,922,007. In addition to the mono, di, and trisodium salts, other pharmaceutically acceptable salts of bisphosphonic acids that may be employed in the present invention include ammonium salts, alkali metal salts such as potassium, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine and so forth. The salts may be prepared by methods known in the art, such as in U.S. Patent No. 4,922,077.

B. Novel Enteric-Coated Oral Dosage Form For Delivery of the  
Bisphosphonic Acid Active Ingredient to the Lower Intestine

As stated hereinabove, the present invention is directed to a novel enteric-coated oral dosage form of the bisphosphonic acid active ingredient to effect delivery to the lower intestine of a human or other mammal, preferably to the small intestine, of a pharmaceutical composition comprised of a therapeutically effective amount of about 0.1-500 mg of a bisphosphonic acid active ingredient and pharmaceutically accepted excipients.

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5       The term "pharmaceutically-acceptable excipients" as used herein includes any physiologically inert, pharmacologically inactive material known to one skilled in the art, which is compatible with the physical and chemical characteristics of the particular bisphosphonic acid selected for use.

### CORE TABLETS

10       Core tablets of the present invention may be formed by combining the bisphosphonic acid active ingredient with pharmaceutically-acceptable excipients in a mixture including, but not limited to:

15           a diluent,  
          a binder,  
          a disintegrant,  
          and optionally one or more ingredients selected from a group consisting of: compression aids, flavors, flavor enhancers, sweeteners, dyes, pigments, buffer systems, and preservatives; lubricating the mixture with a lubricant; and compressing the resultant lubricated mixture into a desired tablet form using various tableting techniques available to those skilled in the art. The term "tablet" as used  
20       herein is intended to encompass compressed pharmaceutical dosage formulations of all shapes and sizes.

25       Particular diluents employable in the present invention include, but are not limited to, lactose. In particular anhydrous lactose is preferred.

          Particular binders employable in the present invention include, but are not limited to, microcrystalline cellulose. Microcrystalline cellulose is available under the trade name "Avicel" from FMC Corporation.

30       The disintegrant may be one of several modified starches, or modified cellulose polymers, in particular, crosscarmellose sodium is preferred. Crosscarmellose sodium NF Type A is commercially available under the trade name "Ac-di-sol".



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Particular lubricants employable in the present invention include, but are not limited to, magnesium stearate, stearic acid, and talc.

Flavoring agents among those useful herein include those described in *Remington's Pharmaceutical Sciences*, 18th Edition, Mack Publishing Company, 1990, pp. 1288-1300.

Particular sweeteners employable in the present invention include but are not limited to sucrose, saccharin, glucose, and aspartame.

Dyes and pigments among those useful include those described in the *Handbook of Pharmaceutical Excipients*, pp. 81-90, 1986 by the American Pharmaceutical Association & the Pharmaceutical Society of Great Britain.

Particular preservatives employable in the present invention include, but are not limited to methyl paraben, propyl paraben, cetylpyridinium chloride, and the salts thereof, sorbic acid and the salts thereof, thimerosal, and benzalkonium chloride.

Although core tablets of the present invention may be prepared using conventional technology and pharmaceutically-acceptable excipients, standard methods for tablet formulation of bisphosphonic acids suffer from serious difficulties. In particular, bisphosphonic acids which bear a basic nitrogen-containing moiety may interact with the lactose of standard formulations resulting in instability and loss of potency. This degradation is particularly pronounced in the presence of water. An application corresponding to Serial No. 07/984,399 has been filed which discloses a dry mix formulation for tablets containing bisphosphonic acids and a process for the preparation of such tablets which eliminates the above mentioned problems by avoiding interaction between the bisphosphonic acid and lactose in the formulation. This process is preferred for preparation of core tablets in the present invention.

#### ENTERIC COATING

The term "enteric-coating" as used herein relates to a mixture of pharmaceutically acceptable excipients which is applied to the core tablet containing the bisphosphonic acid active ingredient and

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which prevents release of said active ingredient in the mouth, esophagus or stomach, but which rapidly and completely releases the drug when the dosage form passes into the proximal portion of the lower gastrointestinal tract.

5 Any conventional enteric film forming polymer or mixture of polymers which is insoluble at a pH below 5.5, i.e., that generally found in the mouth, esophagus, and stomach, but soluble at pH 5.5 or above, i.e., that present in the small intestine and the large intestine, can be used in the present invention.

10 Particular enteric film forming polymers employable in the present invention include but are not limited to cellulose acetate phthalate, methyl acrylate-methacrylic acid copolymers, cellulose acetate succinate, hydroxypropylmethylcellulose phthalate, polyvinyl acetate phthalate, and methyl methacrylate-methacrylic acid copolymers.

15 Of these, we particularly prefer to use anionic carboxylic copolymers based on methacrylic acid and methacrylate, commercially available as Eudragit®. A particularly suitable methacrylic acid copolymer is Eudragit L-30-D®, manufactured by Rohm Pharma GmbH, Weiterstadt, West Germany. Eudragit L-30-D® has a ratio of free  
20 carboxyl groups to ester groups of approximately 1:1 and is freely soluble at pH 5.5 and above as typically present in the small intestine and the large intestine. In general, the greater the percentage of Eudragit L-30-D® contained in the enteric coating of the present invention, the more proximal the release of active in the lower gastrointestinal tract.  
25 The location in the lower gastrointestinal tract at which said coatings release the active can be manipulated by one skilled in the art through control of the composition and thickness of the applied enteric coating.

In order to function properly as an enteric coating, the polymer film must be essentially free from pores or cracks which would  
30 permit penetration of the gastric fluids. The propensity of the film to crack is reduced by using a plasticizer. Although the nature of such plasticizers is restricted by the requirement that they should be safe to administer to mammalian organisms, a wide range of compounds may be used as a plasticizer in practice of the present invention.

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Particular plasticizing agents employable in the present invention include, but are not limited to propylene glycol, glycerol, glyceryl triacetate, polyethylene glycol, triethyl citrate, tributyl citrate, diethyl phthalate, and dibutyl phthalate.

5 Other additives such as talc or silica may be used as detackifiers to improve the coating process.

### SUBCOATING

10 In order to rapidly and completely deliver the bisphosphonic acid active ingredient to the proximal portion of the lower gastrointestinal tract, preferably the small intestine, it is important that the enteric film not be so thick as to impede complete dissolution and release of the active ingredient in the small intestine.

15 The novel enteric-coated dosage forms embodied in the present invention incorporate a stability enhancing subcoat which in addition to minimizing interaction between active drug and the acidic enteric coating also permits utilization of a single 10-200 micron thick enteric film without compromising product stability. This subcoat inhibits migration of active ingredient from core tablet to the enteric  
20 coating, thus improving shelf life and product stability, but rapidly dissolves in intestinal fluid once the enteric coating has been breached.

Particular subcoating polymers employable in the present invention include, but are not limited to hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxypropyl ethylcellulose, and  
25 polyvinylpyrrolidone.

The following are specific embodiments to teach the practice of the disclosed invention but not to limit its scope. For these specific examples, alendronate monosodium trihydrate is used as the therapeutic bisphosphonate compound incorporated in the core tablet. The amount of  
30 alternative bisphosphonate compounds would, of course, be adjusted according to the relative potency and therapeutic effectiveness of the particular compound. The amounts of the enteric-coating components would therefore be adjusted so that a thin, 10-200 micron film of the enteric coating polymer can be uniformly applied over the surface of the

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tablets. All film coats are atomized and deposited onto the core tablets from aqueous dispersions containing between 1-30% solids using conventional pharmaceutical technology.

5

EXAMPLE 1

		<u>mg alendronate/tablet</u>		
<u>Subcoat</u>		<u>5 mg</u>	<u>25 mg</u>	<u>50 mg</u>
10	Hydroxypropyl Methylcellulose 6 cP	4.0	4.0	6.0
<u>Functional Coating</u>				
	Eudragit L30D (methacrylic acid copolymer, type C, NF)	12.1*	12.1*	18.1*
	Triacetin, USP	1.3	1.3	2.0
15	Polyethylene Glycol, USP	2.0	2.0	3.0
	Talc, USP	2.4	2.4	3.6
	Xanthan Gum, NF	0.2	0.2	0.3
20	FUNCTIONAL FILM WEIGHT:	18.0 mg	18.0 mg	27.0 mg

EXAMPLE 2

		<u>mg alendronate/tablet</u>		
<u>Subcoat</u>		<u>5 mg</u>	<u>25 mg</u>	<u>50 mg</u>
25	Hydroxypropyl Methylcellulose 6 cP	4.0	4.0	6.0
<u>Functional Coating</u>				
	Eudragit L30D (methacrylic acid copolymer, type C, NF)	12.7*	12.7	19.0*
30	Polyethylene Glycol 400	1.3	1.3	2.0
	FUNCTIONAL FILM WEIGHT:	14.0 mg	14.0 mg	21.0 mg

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EXAMPLE 3

		<u>mg alendronate/tablet</u>		
<u>Subcoat</u>		<u>5 mg</u>	<u>25 mg</u>	<u>50 mg</u>
5	Hydroxypropyl Methylcellulose 6 cP	4.0	4.0	6.0
<u>Functional Coating</u>				
	Eudragit L30D (methacrylic acid			
	copolymer, type C, NF)	12.7*	2.7*	19.0*
10	Polyethylene Glycol 3350	<u>2.0</u>	<u>2.0</u>	<u>3.0</u>
FUNCTIONAL FILM WEIGHT:		14.7 mg	14.7 mg	22.0 mg

EXAMPLE 4

		<u>mg alendronate/tablet</u>		
<u>Subcoat</u>		<u>5 mg</u>	<u>25 mg</u>	<u>50 mg</u>
15	Hydroxypropyl Methylcellulose 6 cP	4.0	4.0	6.0
<u>Functional Coating</u>				
	Eudragit L30D (methacrylic acid			
	copolymer, type C, NF)	12.7*	12.7*	19.0*
20	Triethylcitrate	<u>1.3</u>	<u>1.3</u>	<u>2.0</u>
FUNCTIONAL FILM WEIGHT:		14.0 mg	14.0 mg	21.0 mg

30

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EXAMPLE 5

		<u>mg alendronate/tablet</u>		
		<u>5 mg</u>	<u>25 mg</u>	<u>50 mg</u>
5	<u>Subcoat</u>			
	50:50 Hydroxypropyl Methylcellulose/ Hydroxypropyl cellulose	4.0	4.0	6.0
		<u>Functional Coating</u>		
10	Eudragit L30D (methacrylic acid copolymer, type C, NF)	12.7*	12.7*	19.0*
	Triethylcitrate	<u>1.3</u>	<u>1.3</u>	<u>2.0</u>
	FUNCTIONAL FILM WEIGHT:	14.0 mg	14.0 mg	21.0 mg

15 \* Dry weight. The commercial product is available as a 30% dispersion so that the corresponding amounts of dispersion used to obtain dry weights of 12.7 and 19.0 mg are 42.3 and 62.7 mg respectively.

20 From the foregoing, other typical acceptable pharmaceutical formulations will be apparent to those skilled in the art of pharmaceutical formulations. While this invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and

25 substitutions can be made therein without departing from the spirit of the invention. For example, enteric-coated tablets or granules of the present invention may placed in gelatin capsules along with other medicants to be administered to a mammalian organism. Accordingly, such expected variations or differences in the practice of the present invention are

30 contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow.

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WHAT IS CLAIMED IS:

1. An enteric-coated oral dosage form comprising:

- 5 (i) a core tablet or granules containing a therapeutically effective amount of a bisphosphonic acid compound having the Formula (I)



(I)

15 or a pharmaceutically acceptable salt thereof, wherein:

R<sup>1</sup> is

- (a) C<sub>1-5</sub> alkyl, unsubstituted or substituted with:
- 20 (1) NH<sub>2</sub>,  
 (2) pyridyl,  
 (3) pyrrolidyl,  
 (4) NR<sup>3</sup>R<sup>4</sup>,
- (b) NR<sup>5</sup>,
- (c) SR<sup>6</sup>,
- 25 (d) Cl;

R<sup>2</sup> is H, OH, Cl;

R<sup>3</sup> is H, C<sub>1-4</sub> alkyl;

R<sup>4</sup> is C<sub>1-4</sub> alkyl;

30 R<sup>5</sup> is C<sub>1-10</sub> alkyl;

R<sup>6</sup> is aryl; and

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(ii) an enteric coating consisting of a polymer or mixture of polymers insoluble at a pH below 5.5, but freely soluble at pH 5.5 or above; and

5 (iii) a subcoat comprising a pH independent polymeric film applied to said core tablet or granule so as to inhibit the migration of bisphosphonic acid active ingredient from core tablet to the outer enteric coating.

10

2. The dosage form of Claim 1 wherein the bisphosphonic acid active ingredient is selected from the group consisting of:

- 15 (a) Alendronic Acid,  
(b) Etidrononic Acid,  
(c) Clodronic Acid,  
(d) Pamidronic Acid,  
(e) Tiludronic Acid,  
(f) Risedronic Acid,  
20 (g) 6-Amino-1-hydroxyhexylidene-bisphosphonic acid,  
(h) 1-Hydroxy-3(methylpentylamino)-propylidene bisphosphonic acid;

or any pharmaceutically acceptable salt thereof.

25

3. The dosage form of Claim 1 wherein the amount of bisphosphonic acid active ingredient contained in the core tablet is between 0.1 and 500 mg.

4. The dosage form of Claim 1 or 3 wherein the  
30 bisphosphonic acid active ingredient is the monosodium trihydrate salt of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid.

5. The dosage form of Claim 1, 2, 3 or 4 wherein said



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enteric coating is comprised of anionic carboxylic copolymers based on methacrylic acid and methacrylate wherein the ratio of free carboxyl groups to ester groups is about 1:1.

5           6.     The dosage form of Claim 1, 2, 3, 4 or 5 wherein said polymeric subcoat is comprised of hydroxypropyl methylcellulose.

          7.     The dosage form of Claim 1, 2, 3, 4 or 5 wherein said polymeric subcoat is comprised of a 50:50 mixture of hydroxypropyl methylcellulose and hydroxypropyl cellulose.

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/66 A61K31/675 A61K9/28

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 421 921 (CIBA-GEIGY AG) 10 April 1991 see claims see examples	1-7
Y	WO,A,93 09785 (PROCTER & GAMBLE PHARMACEUTICALS INC.) 27 May 1993 cited in the application see claims see examples	1-7
P,Y	WO,A,93 21907 (LEIRAS OY) 11 November 1993 see claims see examples	1-7

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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## INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0421921	10-04-91	AU-B- 623036	30-04-92
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